Form PTO 1390 (REV 5-93) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P50951
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U S APPLICATION NO (If known, see 37 C F.R. 1.5) 10/088283
INTERNATIONAL APPLICATION NO. PCT/US00/25386	INTERNATIONAL FILING DATE 15 September 2000	PRIORITY DATE CLAIMED 17 September 1999
TITLE OF INVENTION USE OF CSAIDS IN RHINOVIRUS INFECTION		
APPLICANT(S) FOR DO/EO/US Susan B. DILLON and Sandra D. GRIEGO		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/US00/25386, filed September 15, 2000, which claims benefit from the following Provisional Application: 60/154,494, filed September 17, 1999.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper

19. [ ] Other items or information:

10088283 .031302

JC10 Rec'd PCT/PTO 13 MAR 2002

US APPLICATION NO. (if known see 37 CFR 1.50) 10/088283	INTERNATIONAL APPLICATION NO PCT/US00/25386	ATTORNEYS DOCKET NO P50951

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1 492) **$710.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO..... ...**$1,040.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$710.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**25 - 20 =**	**5**	**5 x $18.00**	**$90.00**	
Independent claims	**2 - 3 =**	**0**	**0 x $84.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$800.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$800.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$800.00**	
				Amount to be refunded	$
				charged	$

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$800.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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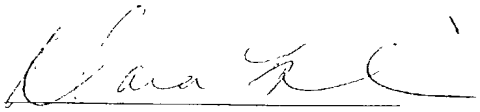

SIGNATURE
Dara L. Dinner
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33,680
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EXPRESS MAIL CERTIFICATE: EV000522418US
DATE OF MAILING: 13 March 2002

PATENT
ATTORNEY'S DOCKET NUMBER **P50951**

TRANSMITTAL LETTER TO THE U.S. DESIGNATED OFFICE
(DO/US) - ENTRY INTO NATIONAL STAGE UNDER 35 USC 371

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/US00/25386	**15 September 2000**	**17 September 1999**

TITLE OF INVENTION
USE OF CSAIDS IN RHINOVIRUS INFECTION

APPLICANT(S) FOR DO/US
Susan B. DILLON and Sandra D. GRIEGO

Box PCT
Commissioner of Patents and Trademarks
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to calculation of the filing fees and examination of the above noted application, entrance of the following remarks and amendments into the record is respectfully requested.

In the Claims:
Please amend the following claims: 8, 10, 15-17, 23-25.

8. (Amended) The method according to Claim 1 wherein the CSBP/p38 inhibitor is administered with a second therapeutic agent.

10. (Amended) The method according to Claim 1 wherein the therapeutic agent is administered orally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation.

15. (Amended) The method according to Claim 1 wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

16. (Amended) The method according to Claim 1 wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

17. (Amended) The method according to Claim 1 wherein the compound is VX-745, RWJ 67657, RWJ-68354, ZM 336372, SU 4984 or RPR-200765A.

23. (Amended) The method according to Claim 18 wherein the CSBP/p38 inhibitor is selected from a compound disclosed in US Patent 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 5,716,955, WO 98/25619, WO 97/25048, WO 99/01452, WO 97/25047, WO 99/01131, WO 99/01130, WO 97/33883, WO 97/35856, WO 97/35855, WO 98/06715, WO 98/07425, WO 98/28292,WO 98/56377 , WO 98/07966 , WO 99/01136 , WO 99/17776 , WO 99/01131 , WO 99/01130, WO 99/32121, WO 00/26209, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 00/18738, WO 00/17175, WO 99/17204, WO 00/20402, WO 99/64400, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/39116, WO 00/43384, WO 00/41698, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/7966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098 , WO 99/00357, WO 98/47892, WO 98/47899, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852, WO 92/12154, WO 94/19350, WO 99/15164, WO 98/50356, DE 19842833, or JP 2000 86657.

24. (Amended) The method according to Claim 18 wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

25. (Amended) The method according to Claim 18 wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

REMARKS

This Preliminary Amendment is being made upon entry of International Application No. PCT/US00/25386 in the U.S. §371 national phase of prosecution. Claims 8, 10, 15-17, and 23-25 have been amended to remove multiple dependency and to conform to US Practice. Claims 1-25 are in the application. Applicants reserve the right to file continuation application on deleted or cancelled subject matter.

A marked version of the amended claims accompanies this paper.

An abstract on a separate sheet of paper accompanies this request.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

Dara L. Dinner
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MARKED UP VERSION OF CLAIMS TO SHOW CHANGES MADE

8. (Amended) The method according to [any one of] Claim[s] 1 [to 7] wherein the CSBP/p38 inhibitor is administered with a second therapeutic agent.

10. (Amended) The method according to [any one of] Claim[s] 1 [to 7] wherein the therapeutic agent is administered orally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation.

15. (Amended) The method according to [c]Claim 1 [to 14] wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

16. (Amended) The method according to [c]Claim 1 [to 14] wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

17. (Amended) The method according to Claim 1 [or 14] wherein the compound is VX-745, RWJ 67657, RWJ-68354, ZM 336372, SU 4984 or RPR-200765A.

23. (Amended) The method according to [any one of] Claim[s] 18 [to 22] wherein the CSBP/p38 inhibitor is selected from a compound disclosed in US Patent 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 5,716,955, WO 98/25619, WO 97/25048, WO 99/01452, WO 97/25047, WO 99/01131, WO 99/01130, WO 97/33883, WO 97/35856, WO 97/35855, WO 98/06715, WO 98/07425, WO 98/28292,WO 98/56377 , WO 98/07966 , WO 99/01136 , WO 99/17776 , WO 99/01131 , WO 99/01130, WO 99/32121, WO 00/26209, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 00/18738, WO 00/17175, WO 99/17204, WO 00/20402, WO 99/64400, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/39116, WO 00/43384, WO 00/41698, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/7966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098 , WO 99/00357, WO 98/47892, WO 98/47899, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 95/09853, WO 95/09851, WO 95/09847,

WO 95/09852, WO 92/12154, WO 94/19350, WO 99/15164, WO 98/50356, DE 19842833, or JP 2000 86657.

24. (Amended) The method according to [c]Claim 18 wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazolc, or a pharmaceutically acceptable salt thereof.

25. (Amended) The method according to [c]Claim 18 wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

ABSTRACT

The present invention is directed to the novel use of a CSBP/p38 inhibitor for the treatment of symptoms of the common cold and the exacerbation of symptoms associated therewith in humans.

Use of CSAIDs in Rhinovirus infection

Field of Invention

The present invention relates to the use of a CSBP/p38 inhibitor in the treatment of a CSBP/p38 mediated disease.

Background of the Invention

Human rhinovirus (HRV), the most frequent cause of the common cold, is increasingly associated with more serious sequelae including exacerbation's of asthma, chronic bronchitis, COPD, otitis media, and sinusitis (*Gern et al.*, Clin Micro Reviews 12(1): 9-18 (1999); *Pitkaranta, and Hayden,* Annals of Medicine 30 (6): 529-537 (1998); *Seemungal et al,* ATS abstract "Rhinoviruses are associated with exacerbation's of COPD" (1998)). Recent published studies in adults and adolescents, using PCR to assist in viral detection, have shown that up to 50 to 80% of asthma exacerbation's are associated with upper respiratory tract virus infection, and that rhinovirus is the most common virus (*Atmar et al,* Archives of Internal Medicine. 158 (22): 2453-9 (1998); *Johnston, SL.*, British Medical Journal 310: 1225-9 (1995)). HRV infects nasal epithelial cells; recent evidence suggests the virus may also infect bronchial epithelium. Prodromal cold symptoms are apparent within 24 hours post-infection, peak on days 2 through 5, and resolve within seven to fourteen days; but can be more protracted in some individuals. Symptoms are believed to arise more from the host's response to infection, than an acute cytotoxic effect, since only a small fraction of upper respiratory epithelial cells are demonstrably infected, and there is minimal epithelial cell damage (*Winther et al,* JAMA 256: 1763-1767 (1986). Increased intranasal levels of kinins, IL-1, IL-8, IL-6, IL-11, and neutrophils are found in normal individuals infected with rhinoviruses. A correlation between IL-8 concentration in nasal secretions with local myeloperoxidase levels and with symptom severity has been demonstrated in several recent studies (*Grieff, et al.* Eur Respir J 13: 41-47 (*1999*); *Teren, et al.* Am J Respir Crit Care Med 155: 1362-1366 (*1997*), *Turner, et al.* Clin Infect Dis 26: 840-846 (*1998*). Intranasal concentrations of IL-1 and IL-6 have been correlated with symptom severity as well (*Proud et al,* J. Infect. Dis.169:1007-1013 (*1994*); *Zhu et al,* J. Clin. Invest. 97:421-430 (*1996*)). Experimental rhinovirus infection also results in enhanced immediate and late phase allergic reactions, and in increased infiltration of T lymphocytes and eosinophils into the lower airways. In atopics and

asthmatics, these effects persist for up to 2 months post - infection (*Gern and Busse*, Am J Respir Crit Care Med, 152: S40-S45 (*1995*). Human bronchial epithelial cell lines have been shown to produce IL-1, IL-6, IL-8, IL-11 and GM-CSF in response to rhinovirus infection (*Subauste et al*, J Clin Invest, 96: 549-557 (1995); *Gern et al., supra, 1999)*. Early production of cytokines by rhinovirus - infected epithelial cells may therefore be responsible for triggering recruitment of neutrophils, T cells and activated eosinophils into the upper and lower airways.

In addition, IL-1, IL-6, and IL-8 are also produced in response to infection with other respiratory viruses (influenza, respiratory syncytial virus) which can cause the common cold and associated sequelae.

By interfering with the biochemical processes of epithelial cells resulting from virus infection there represents a viable new therapeutic target by an inhibitor of CSBP/p38. This invention is directed to the novel discovery of treatment of this therapeutic target.

Summary of the Invention

The present invention relates to the use of a CSBP/p38 kinase inhibitor for the treatment, including prophylaxis, of the common cold, or respiratory viral infection caused by human rhinovirus infection (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus infection in a human in need thereof which method comprises administering to said human an effective amount of a CBSP/p38 inhibitor.

Another aspect of the present invention is a method of treating, including prophylaxis of influenza induced pneumonia in a human in need thereof which method comprises administering to said human an effective amount of a CBSP/p38 inhibitor

The present invention also relates to the use of the CSBP/p38 kinase inhibitor for the treatment, including prophylaxis, of inflammation associated with a viral infection of a human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus.

Brief Description of the Drawings

Figure 1 demonstrates Cytokine Production by Rhinovirus infected BEAS-2B cells. Culture supernatants were collected 72 hours post-infection of BEAS-2B cells with rhinovirus-39 (MOI 1). Uninfected cells served as controls. Protein concentrations in supernatants were determined by ELISA (R&D Systems). Results represent the mean concentration values obtained from 6 experiments.

Figure 2 demonstrates Inhibition of cytokines by CSAIDs: BEAS-2B cultures infected with rhinovirus-39 were cultured in the presence of various concentrations of drug. Cytokine levels in supernatant were determined 72 hours post-infection using commercially available ELISA kits. Results are expressed as % inhibition from infected untreated cultures. Cytokine concentrations in infected control cultures were 4902 pg/ml IL-6, 4520 pg/ml IL-8, and 28 pg/ml GM-CSF.

Figure 3 demonstrates Tyrosine phosphorylation of p38 kinase by rhinovirus infection. BEAS-2B cells were incubated with rhinovirus-39 for various times as indicated. Cell lysates were separated by 10% SDS-polyacrylamide gel, transferred to nitrocellulose membrane and probed with specific antibody to phosphorylated p38 kinase (A) or total p38 kinase (B). Amounts of p38 kinase were quantitated by image analyzer and are presented as volumes based on densitometer scans.

Figure 4 demonstrates Tyrosine phosphorylation of p38 kinase by rhinovirus infection. BEAS-2B cells were incubated with various doses (MOI) of rhinovirus-39 for 30 minutes. Cell lysates were separated by 10% SDS-polyacrylamide gel, transferred to nitrocellulose membrane and probed with specific antibody to phosphorylated p38 kinase or total p38 kinase. Amounts of p38 kinase were quantitated by image analyzer and are presented as relative amounts of total or phosphorylated p38 kinase compared to control cells incubated with media alone (fold increase).

Figure 5 demonstrates the effect of Compound VI, 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-[2-phenoxypyrimidin-4-yl]imidazole on improvement of pulmonary function with increasing doses. BALB/c mice were treated from days 3-8 post-infection with a sub-lethal dose of Influenza A. Pulmonary resistance was determined using whole body plethysmography.

Figure 6 demonstrates the effect of Compounds V, 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole and Compound VI, on prevention of weight loss in animals in an in vivo influenza model.

Figure 7 demonstrates the efficacy of of Compounds V and VI at improving arterial blood oxygen levels (%SpO2) upon treatment. SpO2 was determined using daily pulse oximetry.

Detailed Description of the Invention

IL-1, TNF, and other cytokines affect a wide variety of cells and tissues and these cytokines as well as other leukocyte derived cytokines are important and critical inflammatory mediators of a wide variety of disease states and conditions.

The inhibition of these cytokines is of benefit in controlling, reducing and alleviating many of these disease states.

In particular, the present invention is directed to the treatment of a viral infection in a human, which is caused by the human rhinovirus (HRV), other enterovirus, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or an adenovirus. In particular the invention is directed to respiratory viral infections that exacerbate asthma (induced by such infections), chronic bronchitis, chronic obstructive pulmonary disease, otitis media, and sinusitis. While inhibiting IL-8 or other cytokines may be beneficial in treating a rhinovirus may be known, the use of an inhibitor of the p38 kinase for treating HRV or other respiratory viral infections causing the common cold is believed novel.

It should be noted that the respiratory viral infection treated herein may also be associated with a secondary bacterial infection, such as otitis media, sinusitis, or pneumonia.

For use herein treatment may include prophylaxis for use in a treatment group susceptible to such infections. It may also include reducing the symptoms of, ameliorating the symptoms of, reducing the severity of, reducing the incidence of, or any other change in the condition of the patient, which improves the therapeutic outcome.

The mechanism of action for inhibition of a cytokine by a cytokine suppressive anti-inflammatory drug (CSAID) versus inhibition of virus - induced IL-8 production in airway epithelial cells is believed to be different. In the rhinovirus system, IL-8 production, and CSAID inhibition of IL-8 synthesis is independent of IL-1 and TNF production, whereas the published studies have focused on IL-1 and TNF - induced IL-8 production.

It should be noted that the treatment herein is not directed to the elimination or treatment of the viral organism itself but is directed to treatment of the respiratory viral infection that exacerbates other diseases or symptoms of disease, such as asthma (induced by such infections), chronic bronchitis, chronic obstructive pulmonary disease, otitis media, and sinusitis.

The present invention will demonstrate that CSAID inhibitors are useful in the treatment of symptoms associated with HRV, including exacerbations of underlying conditions such as asthma, COPD, sinusitis and otitis media amongst others.

A preferred virus for treatment herein is the human rhinovirus infection (HRV) or respiratory syncytial virus (RSV).

Another aspect of the present invention is a method of treating, including prophylaxis of influenza induced pneumonia in a human in need thereof which method comprises administering to said human an effective amount of a CBSP/p38 inhibitor. Therefore, for this usage, a preferred virus for treatment is the influenza virus.

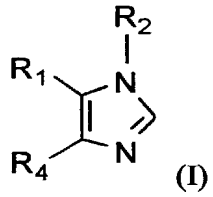
Lastly, another aspect of the present invention relates to the use of a CSBP/p38 kinase inhibitor for the treatment, including prophylaxis, of inflammation associated with a viral infection of a human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus. Preferably the viral infection is HRV or RSV, or the influenza or parainfluenza virus.

Suitable CSAID compounds are well known in the art, and an assay for determining CBSP/p38 inhibition is also readily available using assays disclosed in the below noted patents or applications. For instance, see US Patents 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, and US 5,716,955; WIPO publications WO 98/25619, WO 97/25048, WO 99/01452, WO 97/25047, WO 99/01131, WO 99/01130, WO 97/33883, WO 97/35856, WO 97/35855, WO 98/06715, WO 98/07425, WO 98/28292, WO 98/56377 , WO 98/07966 , WO 99/01136 , WO 99/17776 , WO 99/01131 , WO 99/01130, WO 99/32121, WO 00/26209, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 00/18738, WO 00/17175, WO 99/17204, WO 00/20402, WO 99/64400, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/35911, WO 00/39116, WO 00/43384, WO 00/41698, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/7966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098 , WO 99/00357, WO 98/47892, WO 98/47899, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 95/09853, WO 99/15164, WO 98/50356; WO 95/09851, WO 95/09847, WO 95/09852, WO 92/12154, WO 94/19350, DE 19842833, JP 2000 86657 and De Laszlo et al., Bioorg. Med. Chem. Lett 8 (1998) 2689-2694 whose disclosures are all incorporated herein by reference in their entirety.

Preferred compounds of this invention include those contained in WO 99/01131, and a representative genus is described below. Also preferred for use herein are the compounds disclosed in WO 99/61426 Scios, Inc.; and those compounds disclosed in WO 98/27098 containing the compound known as VX-745; (also known as 5-(2,6-Dichloro-phenyl)-2-(2,4-difluoro-phenylsulfanyl)-1,7,8a-

triaza-naphthalen-6-one), the Johnson & Johnson compound RWJ-68354 disclosed in WO 98/47899, RPR compound RPR-200765A, the Zeneca compound ZM 336372 disclosed in WO 99/15164; the Sugen compound SU 4984 disclosed in WO 98/50356. A review of various inhibitors of p38 kinase is taught in Boehm et al., Exp. Opin. Ther. Patents 10(1):25-37 (2000).

Compounds of Formula (I) are represented by the formula:



(I)

wherein

R_1 is 4-pyridyl, pyrimidinyl, 4-pyridazinyl, 1,2,4-triazin-5-yl, quinolyl, isoquinolinyl, or quinazolin-4-yl ring, which ring is substituted with Y-R_a and optionally with an additional independent substituent selected from C_{1-4} alkyl, halogen, hydroxyl, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkylsulfinyl, CH_2OR_{12}, amino, mono and di- C_{1-6} alkyl substituted amino, an N-heterocyclyl ring which ring has from 5 to 7 members and optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15}, $N(R_{10})C(O)R_b$ or NHR_a;

Y is oxygen or sulfur;

R_4 is phenyl, naphth-1-yl or naphth-2-yl, or a heteroaryl, which is optionally substituted by one or two substituents, each of which is independently selected, and which, for a 4-phenyl, 4-naphth-1-yl, 5-naphth-2-yl or 6-naphth-2-yl substituent, is halogen, cyano, nitro, $C(Z)NR_7R_{17}$, $C(Z)OR_{16}$, $(CR_{10}R_{20})_vCOR_{12}$, SR_5, SOR_5, OR_{12}, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $ZC(Z)R_{12}$, $NR_{10}C(Z)R_{16}$, or $(CR_{10}R_{20})_vNR_{10}R_{20}$ and which, for other positions of substitution, is halogen, cyano, $C(Z)NR_{13}R_{14}$, $C(Z)OR_3$, $(CR_{10}R_{20})_{m"}COR_3$, $S(O)_mR_3$, OR_3, halo-substituted-C_{1-4} alkyl, C_{1-4} alkyl, $(CR_{10}R_{20})_{m"}NR_{10}C(Z)R_3$, $NR_{10}S(O)_{m'}R_8$, $NR_{10}S(O)_{m'}NR_7R_{17}$, $ZC(Z)R_3$ or $(CR_{10}R_{20})_{m"}NR_{13}R_{14}$;

Z is oxygen or sulfur;

n is an integer having a value of 1 to 10;

m is 0, or the integer 1 or 2;

m' is an integer having a value of 1 or 2,

m" is 0, or an integer having a value of 1 to 5;

v is 0, or an integer having a value of 1 or 2;
R_2 is -C(H) (A) (R_{22});

A is an optionally substituted aryl, heterocyclyl, or heteroaryl ring, or A is a substituted C_{1-10} alkyl;

R_{22} is an optionally substituted C_{1-10} alkyl;

R_a is aryl, arylC_{1-6}alkyl, heterocyclic, heterocyclylC_{1-6} alkyl, heteroaryl, heteroarylC_{1-6}alkyl, wherein each of these moieties may be optionally substituted;

R_b is hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, or heterocyclylC_{1-4} alkyl, wherein each of these moieties may be optionally substituted;

R_3 is heterocyclyl, heterocyclylC_{1-10} alkyl or R_8;

R_5 is hydrogen, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl or NR_7R_{17}, excluding the moieties SR_5 being SNR_7R_{17} and SOR_5 being SOH;

R_6 is hydrogen, a pharmaceutically acceptable cation, C_{1-10} alkyl, C_{3-7} cycloalkyl, aryl, arylC_{1-4} alkyl, heteroaryl, heteroarylC_{1-4}alkyl, heterocyclyl, aroyl, or C_{1-10} alkanoyl;

R_7 and R_{17} is each independently selected from hydrogen or C_{1-4} alkyl or R_7 and R_{17} together with the nitrogen to which they are attached form a heterocyclic ring of 5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR_{15};

R_8 is C_{1-10} alkyl, halo-substituted C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-7} cycloalkyl, C_{5-7} cycloalkenyl, aryl, arylC_{1-10} alkyl, heteroaryl, heteroarylC_{1-10} alkyl, $(CR_{10}R_{20})_nOR_{11}$, $(CR_{10}R_{20})_nS(O)_mR_{18}$, $(CR_{10}R_{20})_nNHS(O)_2R_{18}$, $(CR_{10}R_{20})_nNR_{13}R_{14}$; wherein the aryl, arylalkyl, heteroaryl, heteroaryl alkyl may be optionally substituted;

R_9 is hydrogen, $C(Z)R_{11}$ or optionally substituted C_{1-10} alkyl, $S(O)_2R_{18}$, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl;

R_{10} and R_{20} is each independently selected from hydrogen or C_{1-4} alkyl;

R_{11} is hydrogen, C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, heterocyclyl C_{1-10}alkyl, aryl, arylC_{1-10} alkyl, heteroaryl or heteroarylC_{1-10} alkyl, wherein these moieties may be optionally substituted;

R_{12} is hydrogen or R_{16};

R_{13} and R_{14} is each independently selected from hydrogen or optionally substituted C_{1-4} alkyl, optionally substituted aryl or optionally substituted aryl-C_{1-4} alkyl, or together with the nitrogen which they are attached form a heterocyclic ring of

5 to 7 members which ring optionally contains an additional heteroatom selected from oxygen, sulfur or NR9 ;

R_{15} is R_{10} or C(Z)-C_{1-4} alkyl;

R_{16} is C_{1-4} alkyl, halo-substituted-C_{1-4} alkyl, or C_{3-7} cycloalkyl;

R_{18} is C_{1-10} alkyl, C_{3-7} cycloalkyl, heterocyclyl, aryl, aryl$_{1-10}$alkyl, heterocyclyl, heterocyclyl-C_{1-10}alkyl, heteroaryl or heteroaryl$_{1-10}$alkyl;

or a pharmaceutically acceptable salt thereof.

R_2 is a substituted alkyl derivative. It is recognized that the first methylene carbon in this chain is a tertiary carbon, and it will contain one hydrogen moiety. This methylene group will have has two additional substituents, an R_{22} moiety and an A moiety, -C(H)(A)(R_{22}). Both A and R_{22} may not be unsubstituted C_{1-10} alkyl moieties.

In a preferred embodiment, R_2 is a -C(AA_1)(A) moiety, wherein AA_1 is the R_{22} moiety, but is specifically the side chain residue (R) of an amino acid, as is further described herein.

Suitably, A is an optionally substituted C_{3-7}cycloalkyl, aryl, heteroaryl, or heterocyclic ring, or A is a substituted C_{1-10} alkyl moiety.

When A is an aryl, heteroaryl and heterocyclic ring, the ring may be substituted independently one or more times, preferably, 1 to 3 times by C_{1-10} alkyl; halogen; halo substituted C_{1-10} alkyl, such as CF_3; $(CR_{10}R_{20})_tOR_{11}$; $(CR_{10}R_{20})_tNR_{13}R_{14}$, especially amino or mono- or di-C_{1-4} alkylamino; $(CR_{10}R_{20})_tS(O)_mR_{18}$, wherein m is 0, 1 or 2; SH; $NR_{10}C(Z)R_3$ (such $NHCO(C_{1-10}$ alkyl)); or $NR_{10}S(O)_mR_8$ (such as $NHSO_2(C_{1-10}$ alkyl)).

Suitably, t is 0, or an integer of 1 to 4.

When A is an optionally substituted cycloalkyl it is as defined below with the R_{22} substitution.

When A is an optionally substituted heterocyclyl ring, the ring is preferably a morpholino, pyrrolidinyl, piperazinyl or a piperidinyl ring.

When A is an optionally substituted aryl moiety, it is preferably a phenyl ring.

When A is an optionally substituted heteroaryl ring, it is as defined below in the definition section.

When A is a substituted C_{1-10} alkyl moiety, the alkyl chain may be straight or branched. The chain is substituted independently 1 or more times, preferably 1 to 3 times by halogen, such as fluorine, chlorine, bromine or iodine; halosubstituted C_{1-10} alkyl, such as CF_3; C_{3-7}cycloalkyl, C_{1-10} alkoxy, such as methoxy or ethoxy; hydroxy substituted C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy, such as OCF_2CF_2H;

OR_{11}; $S(O)mR_{18}$ (wherein m is 0, 1 or 2); $NR_{13}R_{14}$; $C(Z)NR_{13}R_{14}$; $S(O)_{m'}NR_{13}R_{14}$; $NR_{23}C(Z)R_{11}$; $NHS(O)_2R_{18}$; $C(Z)R_{11}$; $OC(Z)R_{11}$; $C(Z)OR_{11}$; $C(Z)NR_{11}OR_9$; $N(OR_6)C(Z)NR_{13}R_{14}$; $N(OR_6)C(Z)R_{11}$; $C(=NOR_6)R_{11}$; $NR_{23}C(=NR_{19})NR_{13}R_{14}$; $OC(Z)NR_{13}R_{14}$; $NR_{23}C(Z)NR_{13}R_{14}$; or $NR_{23}C(Z)OR_{10}$.

Preferably A is a C_{3-7} cycloalkyl, or a C_{1-6} alkyl, more preferably a C_{1-2} alkyl, i.e. a methylene or ethylene moiety, more preferably a methylene moiety which is substituted by one of the above noted groups.

Preferably, when A is a C_{1-10} alkyl, it is substituted by OR_{11} where R_{11} is preferably hydrogen, aryl or arylalkyl; $NR_{13}R_{14}$; $OC(Z)R_{11}$; or $C(Z)OR_{11}$.

More preferably, A is substituted by OR_{11} where R_{11} is hydrogen.

Suitably, R_{22} is a C_{1-10} alkyl chain, which chain may be straight or branched and which may be optionally substituted independently, one or more times, preferably 1 to 3 times, by halogen, such as fluorine, chlorine, bromine or iodine; halo substituted C_{1-10} alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; hydroxy substituted C_{1-10} alkoxy; halosubstituted C_{1-10} alkoxy, such as OCF_2CF_2H; OR_{11}; $S(O)_mR_{18}$; $NR_{13}R_{14}$; $C(Z)NR_{13}R_{14}$; $S(O)_{m'}NR_{13}R_{14}$; $NR_{23}C(Z)R_{11}$; $NHS(O)_2R_{18}$; $C(Z)R_{11}$; $OC(Z)R_{11}$; $C(Z)OR_{11}$; $C(Z)NR_{11}OR_9$; $N(OR_6)C(Z)NR_{13}R_{14}$; $N(OR_6)C(Z)R_{11}$; $C(=NOR_6)R_{11}$; $NR_{23}C(=NR_{19})NR_{13}R_{14}$; $OC(Z)NR_{13}R_{14}$; $NR_{23}C(Z)NR_{13}R_{14}$; $NR_{23}C(Z)OR_{10}$; optionally substituted C_{3-7} cycloalkyl; optionally substituted aryl, such as phenyl; optionally substituted heteroaryl; or an optionally substituted heterocyclic. The optional substituents on these cycloalkyl, aryl, heteroaryl, and heterocyclic moieties are as defined herein below.

It is noted that those R_{22} substituent groups which contain carbon as the first connecting group, i.e. $C(Z)OR_{11}$; $C(Z)NR_{11}OR_9$, $C(Z)R_{11}$, $C(Z)NR_{13}R_{14}$, and $C(=NOR_6)R_{11}$, may be the sole carbon in alkyl chain. Therefore, the R_{22} group may, for instance, be a carboxy, an aldehyde, or an amide, as well as being a substituent off a methylene unit, such as carbamoylmethyl, or acetamidomethyl.

Preferably R_{22} is a C_{1-6} unsubstituted or substituted alkyl group, such as a C_{1-3} alkylene, such as methyl, ethyl or isopropyl, or a methylene or ethylene moiety substituted by one of the above noted moieties, or as noted above those substituent groups which contain a carbon may substitutent for the first methylene unit of the alkyl chain, such as carboxy, $C(O)OR_{11}$, $C(O)NR_{13}R_{14}$, or R_{22} is an optionally substituted aryl group, such as a benzyl or phenethyl. In other words, R_{22} can be an optionally substituted alkyl group, or R_{22} can be $C(Z)OR_{11}$, $C(Z)NR_{11}OR_9$, $C(Z)R_{11}$, $C(Z)NR_{13}R_{14}$, or $C(=NOR_6)R_{11}$.

Preferably R_{22} is a C_{1-6} unsubstituted or substituted alkyl group, more preferably a C_{1-2} alkylene chain, such as a methylene or ethylene moiety, more preferably methylene.

Preferably the alkyl chain is substituted by OR_{11}, where R_{11} is preferably hydrogen, aryl or arylalkyl; $S(O)mR_{18}$, where m is 0 and R_{18} is a C_{1-6} alkyl; or an optionally substituted aryl, i.e. a benzyl or phenethyl moiety.

More preferably, R_{22} is phenyl, benzyl, CH_2OH, or CH_2-O-aryl.

Preferably, one or both of A and R_{22} contain hydroxy moieties, such as in C_{1-6} alkyl OR_{11}, wherein R_{11} is hydrogen, i.e.CH_2CH_2OH.

Suitably, when AA_1 is the (R) side chain residue of an amino acid, it is a C_{1-6} alkyl group, which may be straight or branched. This means the R group off the core amino acid of the structure R-C(H)(COOH)(NH_2). The R residue term is for example, CH_3 for alanine, $(CH_3)_2CH$- for valine, $(CH_3)_2CH$-CH_2-for leucine, phenyl-CH_2- for phenylalanine, CH_3-S-CH_2-CH_2- for methionine, etc. All generally recognized primary amino acids are included in this groups, such as but not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tryptophan, tyrosine, valine, hydroxylysine, methylhistidine, and other naturally occurring amino acids not found in proteins, such as β-alanine, γ-aminobutyric acid, homocysteine, homoserine, citrulline, ornithine, canavanine, djenkolic acid, and β-cyanoalanine, or other naturally occurring non-mammalian amino acids.

Preferably AA_1 is the residue of phenylalanine, or alanine.

Preferably, A is a hydroxy substituted C_{1-10} alkyl, and R_{22} is a C_{1-10} alkyl or a hydroxy substituted C_{1-10} alkyl.

For further definitions please refer to the descriptions in WO 99/01131, or in WO 99/01136, *supra*.

A preferred compound for use of 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

Other suitable compounds for use herein include but are not limited to, *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

Methods of using and dosage amounts are the same as those disclosed in the references cited above. See for instance, Adams et al., US patent 5,756,499, issued 26 May 1998. In order to use a compound of formula (I) or a pharmaceutically

acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice.

For all methods of use disclosed herein (or the compounds of Formula (I) and other CSAID compounds), suitably, the daily oral dosage regimen will be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day.

The novel use of CSAID compounds herein may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of CSBP/p38 or cytokine inhibition or production for treatment of influenza pneumonia, and other sequelae associated with viral infection.

The CSBP/p38 inhibitor may also be administered with a second therapeutic agent. The second therapeutic agent may be an antiviral agent such as ribavirin, amantidine, rimantidine, Pleconaril,AG 7088 or BTA-188; it may also be an antiviral agent such as an influenza neuraminidase inhibitor, such as zamanivar (Relenza), oseltamivir (Tamiflu) or RWJ-270201; it may be an antihistamine, such as Benadryl®, chlorpheneramine and salts thereof, brompheneramine or salts thereof, and the generally accepted non-sedating antihistamines, such as loratadine (Claritin®), descarboethoxyloratadine (DCL), fexofenadine (Allegra®), and cetirizine hydrochloride (Zyrtec®) etc., a decongestant, such as phenylpropanolamine and salts thereof, pseudoephedreine or salts thereof; steroids, such as dexamethasone, prednisone, or prenisolone, etc.; various antibiotics, such as the quinolones, cephalosporins, β-lactamase inhibitors, etc.; anti-inflammatory agents, such as an NSAID, a COX-1 or COX-2 inhibitor, ASA, or indomethacin, etc. It is recognized that the above noted agents may be administerd as immediate release, or as extended release dosage forms, either together with a suitable CSAID compound, or seperately. The compositions may be administered sequentially, in combination with, or contemporaneously with a CSAID agent. The administration route of the second agent may also differ from that of the CSAID agent, and hence the dosing schedule may vary accordingly.

Cetirizine HCl manufacture and dosing is described in US Patent 4,525,358; fexofenadine manufacture and dosing is described in US Patents 4,524,129; US 5,375,693; US 5,578,610; US 5,855,912; US 5,932,247; and US 6,037,353.

Loratadine and DCL manufacture and dosing are described in US patent 4,282,233; US 4,371,516; US 4,659,716; US 4,863,931; US 5,314,697; and US 5,595,997.

Zamanivar dosing is disclosed in US Patents 4,627,432; US 4,778,054; US 4,811,731; US 5,035,237; US 5,360,817; and US 5,648,379. Oseltamivir dosing is disclosed in US Patents US 5,763,483; US 5,866,601; and US 5,952,375.

The CSPB/p38 inhibitor may be administered systemically or non-systemically, such as orally, bucally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation. As noted above, the second therapeutic agent may be administered by any suitable means, including parenteral, suppository, etc. which means of administration is not necessarily by the same route, nor concurrent therewith.

As used herein "topically" shall include non-systemic administration. This includes the application of a compound externally to the epidermis or the buccal cavity and/or the instillation of such a compound into the ear, eye and nose.

As used herein "systemic administration" refers to oral, intravenous, intraperitoneal and intramuscular administration, subcutaneous intranasal, intrarectal, or intravaginal.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a CSBP/p38 inhibitor will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a CSBP/p38 inhibitor given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Methods:

Cell lines, rhinovirus serotype 39, and influenza virus A/PR/8/34 were purchased from American Type Culture Collection (ATCC). BEAS-2B cells were cultured according to instructions provided by ATCC using BEGM (bronchial epithelial growth media) purchased from Clonetics Corp. HELA cell cultures, used for detection and titration of virus, were maintained in Eagle's minimum essential media containing 10% fetal calf serum, 2mM l-glutamine, and 10 mM HEPES buffer (MEM).

A modification of the method reported by Subauste et al., *Supra*, for in vitro infection of human bronchial epithelial cells with rhinovirus was used in these studies. BEAS-2B cells ($2x10^5$/well) were cultured in collagen-coated wells for 24 hours prior to infection with rhinovirus. Rhinovirus serotype 39 was added to cell

cultures for one hour incubation at 34°C after which inoculum was replaced with fresh media and cultures were incubated for an additional 72 hours at 34°C. Supernatants collected at 72 hours post-infection were assayed for cytokine protein concentration by ELISA using commercially available kits (R&D Systems). Virus yield was also determined from culture supernatants using a microtitration assay in HELA cell cultures (*Subauste et al., supra 1995*). In cultures treated with p38 kinase inhibitors, drug was added 30 minutes prior to infection. Stocks of compounds were prepared in DMSO (10 mM drug) and stored at -20°C.

For detection of p38 kinase, cultures were incubated in basal media without growth factors and additives to reduce endogenous levels of activated p38 kinase. Cells were harvested at various timepoints after addition of rhinovirus. Detection of tyrosine phosphorylated p38 kinase by immunoblot was analyzed by a commercially available kit and was performed according to the manufacturer's instructions (PhosphoPlus p38 MAPK Antibody Kit: New England BioLabs Inc.).

In some experiments, BEAS-2B cells were infected with influenza virus (strain A/PR/8/34) in place of rhinovirus. Culture supernatant was harvested 48 and 72 hour post-infection and tested by ELISA for cytokine as described above.

Cells and Virus: Influenza A/PR/8/34 sub type H1N1 (VR-95 American Type Culture Collection, Rockville, MD) was grown in the allantoic cavity of 10 day old chicken eggs. Following incubation at 37°C, and refrigeration for 2 1/2 hours at 4°C, allantoic fluid was harvested, pooled, and centrifuged (1,000 rcf; 15 min; 4°C) to remove cells. Supernatent was aliquoted and stored at -70°C. The titer of the stock culture of virus was 1.0×10^{10} Tissue Culture Infective Dose/ml ($TCID_{50}$)

Inoculation procedure: Four-six week old female Balb/cAnNcrlBr mice were obtained from Charles River, Raleigh, NC. Animals were infected intranasally. Mice were anesthetized by intraperitioneal injection of Ketamine (40mg/kg; Fort Dodge Labs, Fort Dodge, Ia) and Xylazine (5 mg/kg; Miles, Shawnee Mission, Ks) and then inoculated with 100 TCID50 of PR8 diluted in PBS in 20 ul. Animals were observed daily for signs of infection. All animal studies were approved by SmithKline Beecham Pharmaceuticals Institutional Animal Care and Use Committee.

Virus titration: At various times post infection, animals were sacrificed and lungs were aseptically harvested. Tissues were homogenized, in vials containing 1 micron glass beads (Biospec Products, Bartlesville, OK) and 1 ml. of Eagles minimal essential medium. Cell debris was cleared by centrifugation at 1,000 rcf for 15 minutes at 4°C, and supernatants were serially diluted on Madin-Darby canine kidney (MDCK) cells. After 5 days of incubation at 37°C (5% CO_2), 50 µl of 0.5%

chick red blood cells were added per well, and agglutination was read after 1 hour at room temperature. The virus titer is expressed as 50% tissue culture infective dose ($TCID_{50}$) calculated by logistic regression.

ELISA: Cytokine levels were measured by quantitative ELISA using commercially available kits. Ear samples were homogenized using a tissue minser in PBS. Cell debris was cleared by centrifugation at 14,000 rpm for 5 minutes. The cytokine concentrations and thresholds were determined as described by the manufacturer; IL-6, IFN-γ, and KC (R&D Systems, Minneapolis, MN).

Myeloperoxidase Assay: Myeloperoxidase (MPO) activity was determined kinetically as described by Bradley et al. (1982). Briefly, rabbit cornea were homogenized in Hexadecyl Trimethyl-Ammonium Bromide (HTAB) (Sigma Chemical Co. St. Louis, Mo) which was dissolved in 0.5 m Potassium phosphate buffer (J.T. Baker Scientific, Phillipsburg, NJ). Following homogenization, the samples were subjected to freeze-thaw-sonication (Cole-Parmer 8853, Cole-Parmer, Vernon Hills, Il) 3 times. Suspensions were then cleared by centrifugation at 12,500 x g for 15 minutes at 4°C. MPO enzymatic activity was determined by colormetric change in absorbance during a reaction of O-Dianisidine dihydrochloride (ODI) 0.175 mg/ml (Sigma Chemical Co. St. Louis, Mo) with .0002% Hydrogen peroxide (Sigma Chemical Co. St. Louis, Mo). Measurements were performed by using a Beckman Du 640 Spectrophotometer (Fullerton, Ca.) fitted with a temperature control device. 50 ul of material to be assayed was added to 950 ul of ODI and change in absorbance was measured at a wave length of 460 nm for 2 minutes at 25°C.

Whole Body Plethysomography: Influenza virus infected mice were placed into a whole body plethysomograph box with an internal volume of approximately 350-ml. A bias airflow of one l/min was applied to the box and flow changes were measured and recorded with a Buxco XA data acquisition and respiratory analysis system (Buxco Electronics, Sharon, CT). Animals were allowed to acclimate to the plethysmograph box for 2 min. before airflow data was recorded. Airway measurements were calculated as Penh (enhanced pause). Penh has previously been shown as an index of airway obstruction and correlates with increased intrapleural pressure. The algorithm for Penh calculation is as follows: Penh = [(expiratory time / relaxation time)-1] x (peak expiratory flow / peak inspiratory flow) where relaxation time is the amount of time required for 70% of the tidal volume to be expired.

Determination of arterial oxygen saturation. A Nonin veterinary hand held pulse oximeter 8500V with lingual sensor (Nonin Medical, Inc., Plymouth MN) was used

to determine daily arterial oxygen saturation %SpO2 as described (Sidwell et al. 1992 Antimicrobial Agents and Chemotherapy 36:473-476).

Results:

Inhibition of cytokine production by specific inhibitors of p38 MAP kinase: Consistent with published reports, IL-6, IL-8, and GM-CSF were detected 72 hours post-infection of BEAS-2B cells with rhinovirus-39 (multiplicity of infection; MOI 1.0) (figure 1). Production of IL-6, IL-8, and GM-CSF was not mediated through IL-1 or TNF produced in response to rhinovirus infection since addition of neutralizing antibodies to IL-1 and TNF to the infected cultures did not reduce the amount of IL-6, IL-8 or GM-CSF produced (not shown). Productive infection of cells was confirmed by titering infectious supernatants from BEAS-2B cells on HELA monolayers. There was low but consistent replication of virus during the 72 hour culture period resulting in 1.22 ± 0.3 $\log_{10}$ $TCID_{50}$ increase over the initial input inoculum (n=6 experiments). To investigate the role of p38 kinase signal transduction in rhinovirus-induced cytokine production by epithelial cells, specific p38 kinase inhibitors SB203580, Compound II, Compound III, and an inactive analog, SKF106978, were tested for their ability to inhibit cytokine production in rhinovirus-infected BEAS-2B cell cultures. The compound (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole is alternatively referred to as SB 203580 and may be found in US patent 5,656,644. The compound *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole also known as Compound II may be found in WO 97/25048. The compound 4-(4-Fluorophenyl-5-[(2-phenylamino)pyrimidin-4-yl]-1-(piperdin-4-yl)imidazole, also known as Compound III may be found in US Patent 5,658,903. The compound 2-(4-Methylsulfinyl)-3-[4-(2-methylpyridyl]-6,7-dihydro[5H]pyrrolo[1,2-a]imidazole, is also known as SB 106978. Concentrations of IL-8, IL-6 and GM-CSF in culture supernatants from infected cells treated with inhibitors were all lower than those from untreated infected cultures (figure 2). IL-6 was the most sensitive to inhibition with significant inhibition (40%) being observed with SB 203580 concentrations as low as 30 nM . GM-CSF was the least sensitive to inhibition by SB 203580, with an IC_{50} of approximately 4 uM.

Another inhibitor of p38 kinase, Compound II, was slightly more potent in inhibiting GM-CSF with an IC_{50} of approximately 1 uM. Compound II was comparable to SB 203580 in inhibiting IL-6 and IL-8 production. As expected based on the relative potency of these compounds in specific binding to p38 kinase (data shown in legend box), cytokine inhibition was greatest with Compound III,

with an IC50 value < 10 nM for IL-6, while SKF106978 was inactive at all concentrations tested. Maximum effect obtained by any of the p38 kinase inhibitors against any of the three cytokines was 50% -70% inhibition. The inhibition of cytokine production by CSAIDs was not due to general cell cytotoxicity as determined by standard XTT assays (CC_{50} > 40 uM for all compounds tested) (Roehm et al., J. of Immunol. Methods 142:257-265 (1991).

These compounds also did not exhibit direct antiviral activity as assessed using a standard HELA cell antiviral assay (MIC_{50} > 10 uM for all compounds tested) (Andries et al., Journal of Virology 64(3):1117-1123 (1990) or by measuring virus yield in the RV-infected BEAS-2B cultures directly (not shown).

Activation of p38 kinase by rhinovirus infection:

The presence of tyrosine phosphorylated p38 kinase was measured by immunoblot at various times after the addition of virus to BEAS-2B cultures. Rhinovirus infection of BEAS-2B cells resulted in an increase in phosphorylated p38 kinase that was both dose and time-dependent. Increases in phosphorylated p38 kinase were evident by 15 minutes post exposure to rhinovirus-39 (MOI 10), appeared to peak by 30 minutes after addition of virus and remained elevated 60 minutes post-infection (figure 3). In addition, rhinovirus-induced tyrosine phosphorylation of p38 kinase was dose-dependent (figure 4). When cells were cultured in the absence of virus, there was no increase in the amount of tyrosine phosphorylation of p38 kinase at any of the timepoints tested. Overall levels of p38 kinase protein were comparable between all the groups indicating that virus infection caused phosphorylation of p38 kinase without de novo synthesis of protein (figures 3 and 4).

Effects on in vitro influenza virus infection:

Exposure of BEAS-2B cells with influenza virus (A/PR/8/34; MOI 1.0) also resulted in elaboration of IL-8 and IL-6 as measured 48 - 72 hours post-infection, although the secreted protein levels were lower than that obtained with rhinovirus infection. Consistent with observations in rhinovirus-infected cells, treatment of influenza infected-BEAS-2B cells with p38 kinase inhibitors, Compound IV, 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-[(2-methylphenyl)amino]pyrimidin-4-yl]imidazole and Compound II, 1-*trans*-4-hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole, was also effective in inhibiting IL-6 and IL-8 production.

Effects on in vivo influenza virus infection:

Five (5) independent and reproducible studies demonstrated the efficacy of therapeutic dosing with Compound V, 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole and Compound VI, 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-[2-phenoxypyrimidin-4-yl]imidazole at improving clinical disease in the murine influenza pneumonia model. BALB/c mice were dosed orally b.i.d. on days 3-8 post influenza A/PR8 and monitored daily for weight loss, pulmonary functions and arterial blood oxygen levels $\%Sp0_2$. The antiviral Tamiflu was used as control and demonstrated 47% improvement in pulmonary functions ($p<0.01$ days 5-12), 64% improved $\%Sp0_2$ ($p<0.01$ days 5-18), and prevention of weight loss relative to placebo. The optimal dose of Compound VI was 10 mg/kg leading to 39% improvement in pulmonary functions ($p<0.01$ days 5-12), 30% improvement in $\%Sp0_2$ ($p<0.01$ days 5-13, $p<0.05$ days 14-15), and a similar effect on weight loss as Tamiflu treatment. Efficacy was observed in doses as low as 1 mg/kg: 27% improvement in pulmonary functions ($p<0.01$ days 6-9), 11.6% ($p<0.01$ Days 7-13). At 0.1 mg/kg, we observed 19% improvement in pulmonary functions ($p<0.05$ day 7,8) but no effect on $\%Sp0_2$ or weight loss. At 10 mg/kg, Compound VI was equally effective to Compound V at 30 mg/kg. Samples were collected for evaluation of virus titers and cytokines in lung homogenates. A non-significant trend for inhibition of lung cytokines IL-6, KC, IFN-gamma, and RANTES was observed. There was no negative effect on lung virus titers.

No negative effect on immunity to secondary influenza virus infection: In two studies, mice treated with Compound VI or Compound V during acute PR/8 (H1N1) influenza infection were protected from a lethal challenge with the same virus as demonstrated by 100% survival and normal pulmonary functions. All control primary infection animals died by Day 7. Thus, the CSAIDS have no effect on immunity to a homologous challenge.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without

further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed Is:

1. A method of treating the common cold or respiratory viral infection caused by human rhinovirus (HRV), other enteroviruses, coronavirus, influenza virus, parainfluenza virus, respiratory syncytial virus, or adenovirus in a human in need thereof which method comprises administering to said human an effective amount of a CBSP/p38 inhibitor.

2. The method according to Claim 1 wherein the respiratory viral infection exacerbates asthma.

3. The method according to Claim 1 wherein the respiratory viral infection exacerbates chronic bronchitis.

4. The method according to Claim 1 wherein the respiratory viral infection exacerbates chronic obstructive pulmonary disease.

5. The method according to Claim 1 wherein the respiratory viral infection exacerbates otitis media.

6. The method according to Claim 1 wherein the respiratory viral infection exacerbates sinusitis.

7. The method according to Claim 1 wherein the respiratory viral infection is associated with a secondary bacterial infection, such as otitis media, sinusitis, or pneumonia.

8. The method according to any one of Claims 1 to 7 wherein the CSBP/p38 inhibitor is administered with a second therapeutic agent.

9. The method according to Claim 8 wherein the second therapeutic agent is an antiviral agent selected from ribavirin, amantidine, rimantidine, Pleconaril,AG 7088 or BTA-188; an antihistamine; a decongestant; a steroid; an antibiotic; an anti-inflammatory agent selected from an NSAID, a COX-1 or COX-2 inhibitor, ASA, or indomethacin; an influenza neuraminidase inhibitor selected from zamanivar (Relenza), oseltamivir (Tamiflu) or RWJ-270201.

10. The method according to any one of Claims 1 to 7 wherein the therapeutic agent is administered orally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation.

11. The method according to Claim 10 wherein the CSBP/p38 inhibitor is administered with a second therapeutic agent.

12. The method according to Claim 11 wherein the second therapeutic agent may be administered by a different route than the CSBP/p38 inhibitor.

13. The method according to Claim 12 wherein the second therapeutic agent is an antiviral agent ribavirin, amantidine, rimantidine, Pleconaril, AG 7088, BTA-188; an antihistamine; a decongestant; a steroid; an antibiotic; an anti-inflammatory agent selected from an NSAID, a COX-1 or COX-2 inhibitor, ASA, or indomethacin; or an influenza neuraminidase inhibitor selected from zamanivar (Relenza), oseltamivir(Tamiflu) or RWJ-270201.

14. The method according to Claim 1 wherein the CSBP/p38 inhibitor is selected from a compound disclosed in US Patent 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 5,716,955, WO 98/25619, WO 97/25048, WO 99/01452, WO 97/25047, WO 99/01131, WO 99/01130, WO 97/33883, WO 97/35856, WO 97/35855, WO 98/06715, WO 98/07425, WO 98/28292,WO 98/56377 , WO 98/07966 , WO 99/01136 , WO 99/17776 , WO 99/01131 , WO 99/01130, WO 99/32121, WO 00/26209, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 00/18738, WO 00/17175, WO 99/17204, WO 00/20402, WO 99/64400, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/35911, WO 00/39116, WO 00/43384, WO 00/41698, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/7966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098 , WO 99/00357, WO 98/47892, WO 98/47899, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852,

WO 92/12154, WO 94/19350, WO 99/15164, WO 98/50356, DE 19842833, or JP 2000 86657.

15. The method according to claim 1 or 14 wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

16. The method according to claim 1 or 14 wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

17. The method according to Claim 1 or 14 wherein the compound is VX-745, RWJ 67657, RWJ-68354, ZM 336372, SU 4984 or RPR-200765A.

18. A method of treating the influenza induced pneumonia in a human in need thereof which method comprises administering to said human an effective amount of a CBSP/p38 inhibitor.

19. The method according to Claims 18 wherein the CSBP/p38 inhibitor is administered with a second therapeutic agent.

20. The method according to Claim 19 wherein the second therapeutic agent is an antiviral agent ribavirin, amantidine, rimantidine, Pleconaril, AG 7088, BTA-188; an antihistamine; a decongestant; a steroid; an antibiotic; an anti-inflammatory agent selected from an NSAID, a COX-1 or COX-2 inhibitor, ASA, or indomethacin;or an influenza neuraminidase inhibitor selected from zamanivar (Relenza), oseltamivir (Tamiflu) or RWJ-270201.

21. The method according to Claim 18 wherein the therapeutic agent is administered orally, topically (intranasal) or via inhalation (aerosol), or both topically and via inhalation.

22. The method according to Claim 21 wherein a second therapeutic agent may be administered by a different route than the CSBP/p38 inhibitor.

23. The method according to any one of Claims 18 to 22 wherein the CSBP/p38 inhibitor is selected from a compound disclosed in US Patent 5,716,972, US 5,686,455, US 5,656,644, US 5,593,992, US 5,593,991, US 5,663,334, US 5,670,527, US 5,559,137, 5,658,903, US 5,739,143, US 5,756,499, US 5,716,955, WO 98/25619, WO 97/25048, WO 99/01452, WO 97/25047, WO 99/01131, WO 99/01130, WO 97/33883, WO 97/35856, WO 97/35855, WO 98/06715, WO 98/07425, WO 98/28292,WO 98/56377 , WO 98/07966 , WO 99/01136 , WO 99/17776 , WO 99/01131 , WO 99/01130, WO 99/32121, WO 00/26209, WO 99/58502, WO 99/58523, WO 99/57101, WO 99/61426, WO 99/59960, WO 99/59959, WO 00/18738, WO 00/17175, WO 99/17204, WO 00/20402, WO 99/64400, WO 00/01688, WO 00/07980, WO 00/07991, WO 00/06563, WO 00/12074, WO 00/12497, WO 00/31072, WO 00/31063, WO 00/23072, WO 00/31065, WO 00/39116, WO 00/43384, WO 00/41698, WO 97/36587, WO 97/47618, WO 97/16442, WO 97/16441, WO 97/12876, WO 98/7966, WO 98/56377, WO 98/22109, WO 98/24782, WO 98/24780, WO 98/22457, WO 98/52558, WO 98/52941, WO 98/52937, WO 98/52940, WO 98/56788, WO 98/27098 , WO 99/00357, WO 98/47892, WO 98/47899, WO 99/03837, WO 99/01441, WO 99/01449, WO 99/03484, WO 95/09853, WO 95/09851, WO 95/09847, WO 95/09852, WO 92/12154, WO 94/19350, WO 99/15164, WO 98/50356, DE 19842833, or JP 2000 86657.

24. The method according to claim 18 wherein the compound is 1-(1,3-Dihydroxyprop-2-yl)-4-(4-fluorophenyl)-5-(2-phenoxypyrimidin-4-yl)imidazole, or a pharmaceutically acceptable salt thereof.

25. The method according to claim 18 wherein the compound is *trans*-1-(4-Hydroxycyclohexyl)-4-(4-fluorophenyl)-5-[(2-methoxy)pyrimidin-4-yl]imidazole; 1-(4-Piperidinyl)-4-(4-fluorophenyl)-5-(2-methoxy-4-pyrimidinyl)imidazole; or (4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)-imidazole.

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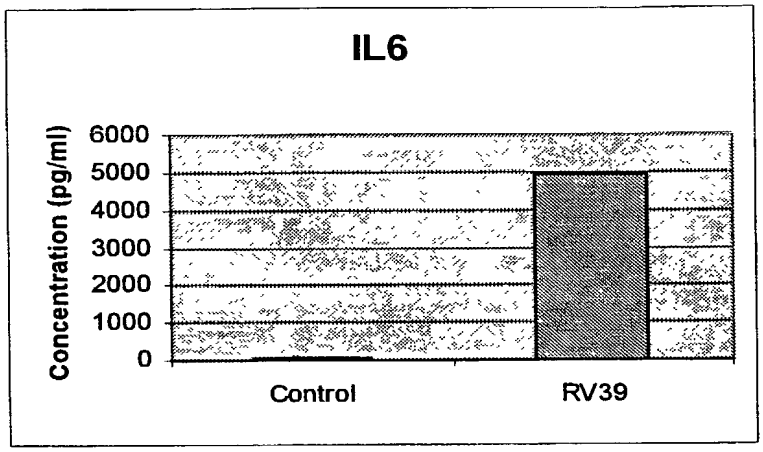
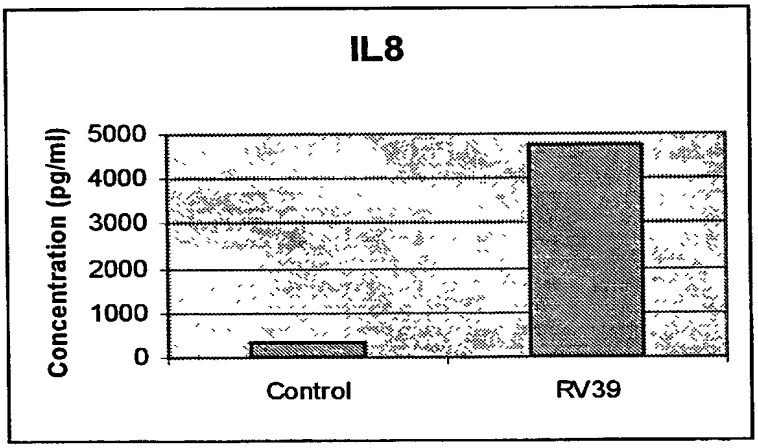
WO 01/19322 A2

(54) Title: USE OF CSAIDS IN RHINOVIRUS INFECTION

(57) Abstract: The present invention is directed to the novel use of a CSBP/p38 inhibitor for the treatment of symptoms of the common cold and the exacerbation of symptoms associated therewith in humans.


IL6
Concentration (pg/ml)
6000
5000
4000
3000
2000
1000
0
Control
RV39


IL8
Concentration (pg/ml)
5000
4000
3000
2000
1000
0
Control
RV39

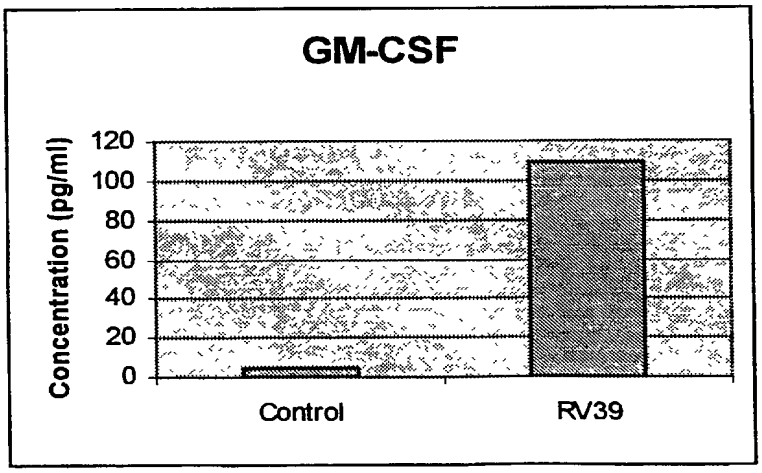
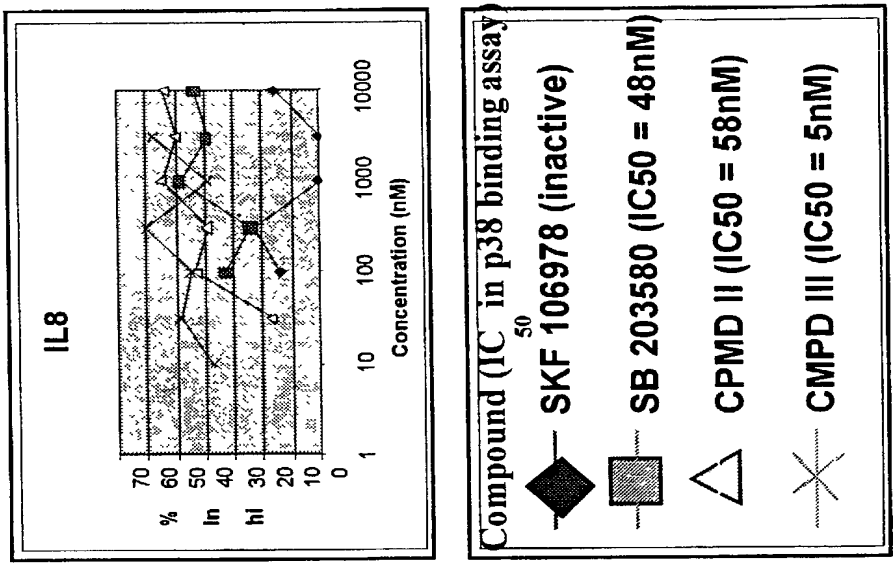

GM-CSF
Concentration (pg/ml)
120
100
80
60
40
20
0
Control
RV39

Figure 1


IL8
% In hi
0 10 20 30 40 50 60 70
1 10 100 1000 10000
Concentration (nM)
Compound (IC50 in p38 binding assay)
SKF 106978 (inactive)
SB 203580 (IC50 = 48nM)
CPMD II (IC50 = 58nM)
CMPD III (IC50 = 5nM)

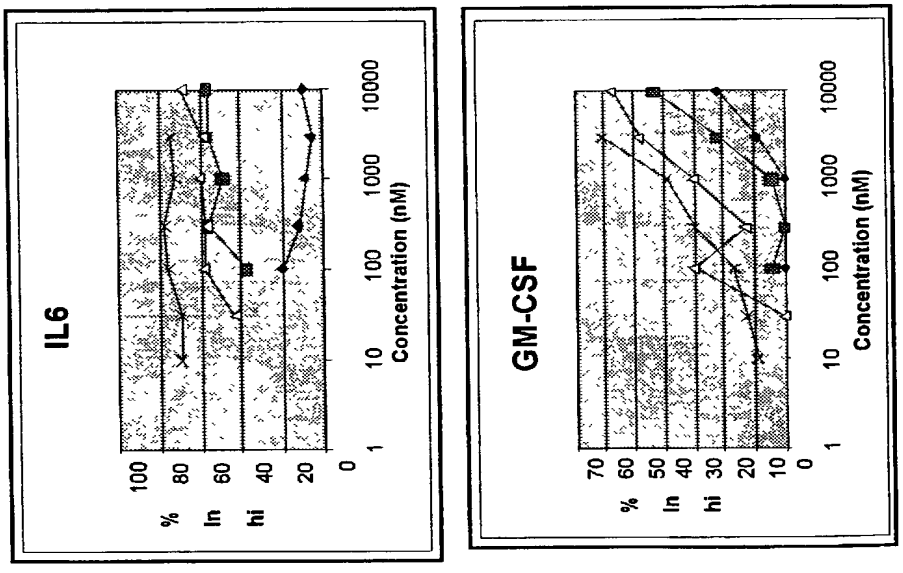
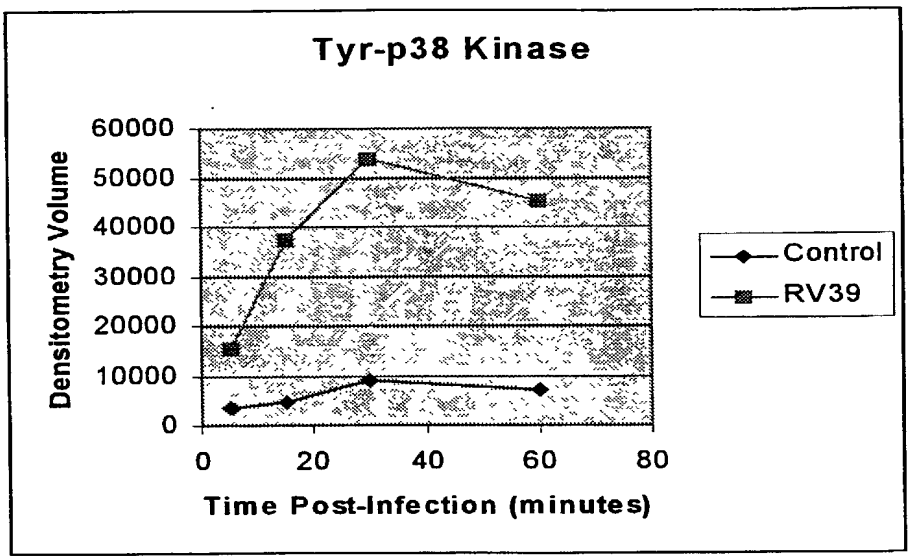

IL6
% In hi
0 20 40 60 80 100
1 10 100 1000 10000
Concentration (nM)
GM-CSF
% In hi
0 10 20 30 40 50 60 70
1 10 100 1000 10000
Concentration (nM)

Figure 2

A.


Tyr-p38 Kinase
Densitometry Volume
60000
50000
40000
30000
20000
10000
0
0
20
40
60
80
Time Post-Infection (minutes)
Control
RV39

B.

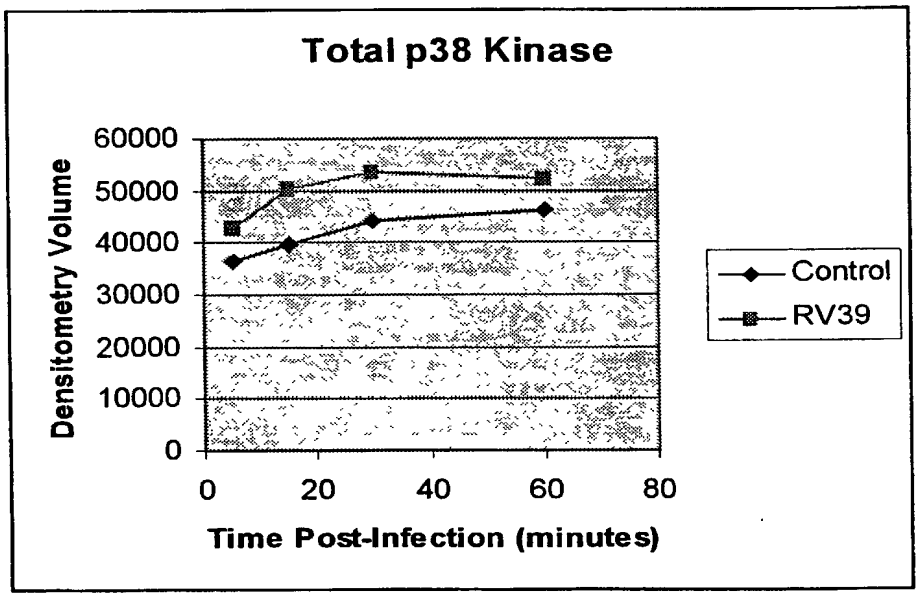

Total p38 Kinase
Densitometry Volume
60000
50000
40000
30000
20000
10000
0
0
20
40
60
80
Time Post-Infection (minutes)
Control
RV39

Figure 3

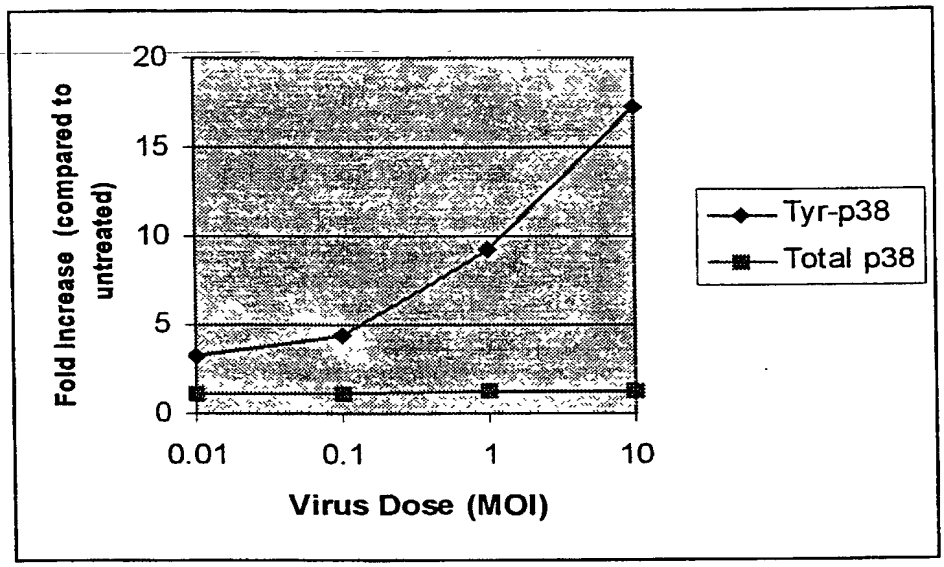

20
15
10
5
0
Fold Increase (compared to untreated)
0.01
0.1
1
10
Virus Dose (MOI)
Tyr-p38
Total p38

Figure 4

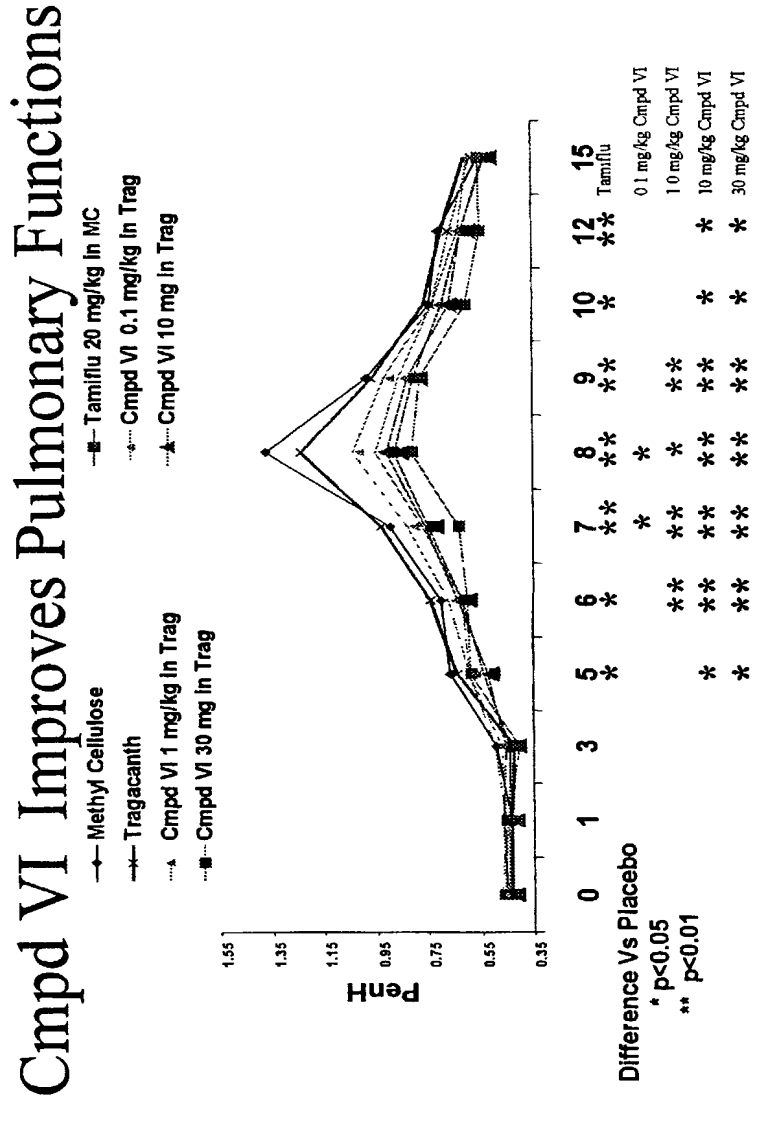


Figure 5

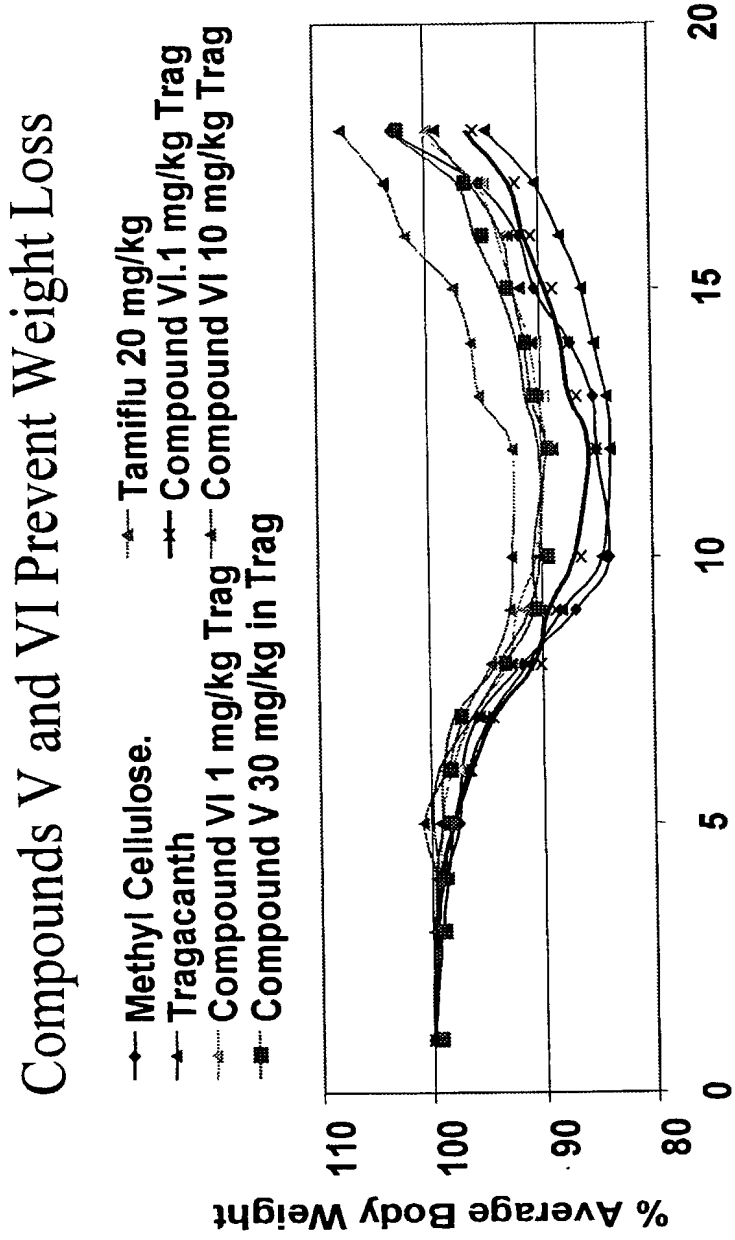

Compounds V and VI Prevent Weight Loss
Methyl Cellulose.
Tragacanth
Compound VI 1 mg/kg Trag
Compound V 30 mg/kg in Trag
Tamiflu 20 mg/kg
Compound VI.1 mg/kg Trag
Compound VI 10 mg/kg Trag
% Average Body Weight
110
100
90
80
0
5
10
15
20
Days Post-Infection

Figure 6

Compounds V and VI Improve Blood Oxygen levels (Pulse Oximetry)

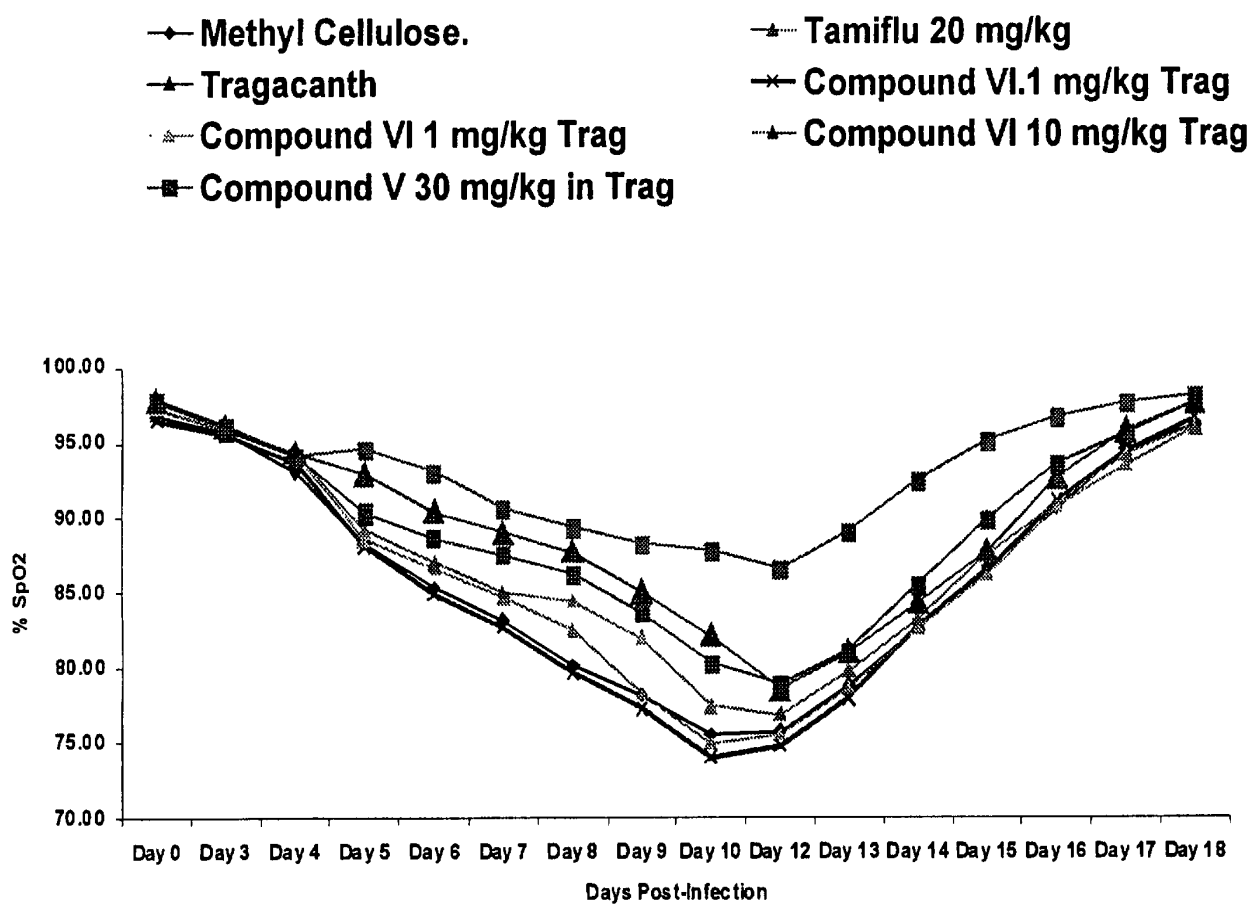


Figure 7

Docket No.: P50951

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

" Use of CSAIDs in Rhinovirus Infection"

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on **15 September 2000** as Serial No. **PCT/US00/25386**
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date
60/154,494	17 September 1999

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT

International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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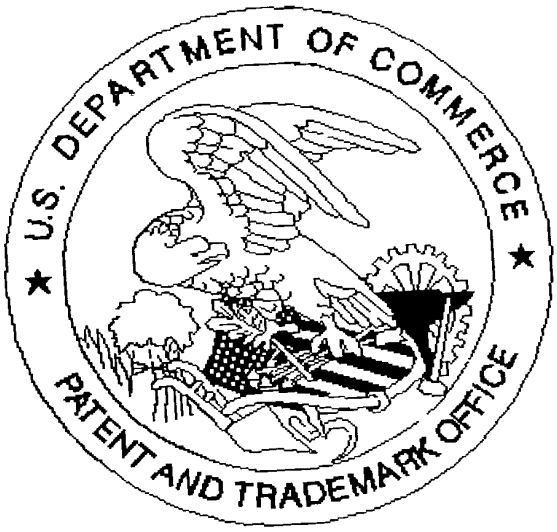

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